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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,257	02/01/2002	Kyogo Itoh	3190-014	8619

33432 7590 12/13/2007

KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
12/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/062,257	ITOH, KYOGO	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/17/07 & 8/20/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44* is/are rejected.

7)☒ Claim(s) *1 and 3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,3,5,9,11,13,15-17,19,21,23,25,27,29,31,33,35,37,39,41,43,44,48,50,52,54,56,58,62,64,66,68,70,72,74,76,77,84,85,88,89,92,93,96,97,100,101,104,105,108,109,112-116 and 122.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,9,11,15,17,19,21,23,25,27,29,31,33,35,37,39,41,43,46,48,50,52,54,56,58,62,64,66,68,70,72,74,76,77,84,85,88,89,92,93,96,97,100,101,104,105,108,109,112-116 and 122.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/17/07 has been entered.

2. Applicant's amendment filed 8/20/07 is acknowledged and has been entered.

3. Applicant is reminded that Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 37 at Table 5 [SEQ ID NO: 10] and page 13 at line 20.

It is noted by the Examiner with regard to the sequence DYLRSV that appears on pages 13 and 36 at the cited locations. Applicant is required to either delete "DYLRSV" while disclosing amino acid residues 1-6, or to provide a separate SEQ ID NO for "DYLRSV" peptide. Whenever a peptide sequence is disclosed by the actual sequence, such as DYLRSV that is a subsequence of SEQ ID NO: 2, rather than by disclosing for example, 'the amino acid sequence of amino acid residues 1-6 of SEQ ID NO: 2', the peptide sequence must have a SEQ ID NO. The Examiner apologizes to Applicant for any inconvenience.

4. Applicant is reminded of Applicant's election with traverse of Group I drawn to the peptide having an amino acid sequence of SEQ ID NO: 1 and pharmaceutical composition thereof in Applicant's response filed 5/24/06.

Claims 1, 3 and 44 are presently being examined as they read on Groups I, II and III (SEQ ID NO: 1-3).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir.1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed pharmaceutical composition recited in instant claim 44, said pharmaceutical composition comprising an effective amount of at least one peptide selected from a peptide of claim 1.

The instant claim encompasses a pharmaceutical composition comprising an amount of at least one of the peptides of claim 1.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

The specification further discloses that the amino acid sequence DYLRSV, common to both SEQ ID NO: 1 and 2, has a relevance to tumor rejection. The specification discloses searching for homologous sequences in other proteins, and testing subseqence 9-mer peptides from some of the tyrosine kinase proteins for binding to HLA-A*2402 and for stimulating CTL (especially Examples 6-7). Larger 13-mer subsequences containing these peptides conform to the formula that is SEQ ID NO: 10 (Example 6).

There are no working examples of any *in vivo* method of treatment with the said peptide. The specification does not does not provide description that administration of the peptide produces such a CTL response that produces a therapeutic effect.

Evidentiary reference Marchand *et al* (Int. J. Cancer 20: 219-230, 1999, of record) teach "Considerable further progress is needed... before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy." (second to last sentence of article).

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001, of record) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies,

immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505). Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000, of record) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000, of record) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endpoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Boon *et al* (Ann. Rev. Immunol. 2006, 24: 175-208, of record) teach "Therapeutic vaccination of metastatic melanoma patients with these antigens [*i.e.,* melanoma antigens] is followed by tumor regressions in only a small minority of the patients (page 175, abstract). Boon *et al* further teach "In conclusion, therapeutic success following vaccination may not depend on the number of T cells produced directly by the vaccine, but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process...To achieve therapeutic success, investigators will probably need to understand the cause of the local immunosuppression in the tumors and find counteracting agents. As stated above, the list of possible immunosuppressive agents present in tumors is considerable. But it will be important to find whether, for each type of tumor, there is a prevalent immunosuppressive agent. Just as many types of tumors have preferred oncogenic pathways that differ from one type of tumor to another, each type of tumor may also have preferred immunosuppressive processes that we must identify to achieve therapeutic success...Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment...We do not believe that melanoma patients suffer from a degree of general immunosuppression, which we believe is restricted to very late-stage patients who are not included in most studies...Therefore, the difference in the quality of the response would be due to a chance event determining, for instance, the functional properties of the unique or the few responder T cell clones elicited by the vaccine. In that case, it will be essential to understand what this crucial functional property is. At the other extreme, the antivaccine T cell responses would be similar in all patients, but the level of resistance of the tumors would vary considerably. In that case investigators would need to identify

the main component of this resistance and find ways to counteract it." (especially pages 193-194).

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in Applicant's amendment filed 8/20/07 on page 16 at the first full paragraph.

Applicant does not address the issue of "pharmaceutical" recited in the instant claim 44, but argues that Applicant has removed the phrase "for cancer treatment" from claim 44. Applicant's argument is not persuasive for the reasons enunciated in the instant rejection.

7. Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention, the claimed pharmaceutical composition recited in instant claim 44, said pharmaceutical composition comprising an effective amount of at least one peptide of claim 1. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the recited pharmaceutical composition can be made and/or used.

The instant claims encompass a pharmaceutical composition comprising an at least one of the peptides of claim 1.

The specification discloses that SEQ ID NO: 1-3 are subsequence peptides of the lck protein that is over-expressed on adenocarcinoma cells or epithelial cancer cells in colon or small cell lung cancers bound to HLA-A2402, exhibited a CTL-activating ability of PBMC from a cancer patient (or PMBC from normal individuals when presented by HLA-A2402 on professional APC dendritic cells), as well as enhancing the production of IFN-γ by CTLs. The specification discloses that CTL induced by the said SEQ ID NO could recognize a tumor cell line (paragraph spanning pages 4-5, page 7 at lines 21-25, paragraph spanning pages 10-11, page 11 at lines 19-24, pages 12-13, Table 1 on page 28, Examples 4-6).

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There are no working examples of any *in vivo* method of treatment with the claimed peptides. The specification does not does not provide disclosure that administration of the peptide *in vivo* produces a CTL response that produces a therapeutic effect.

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success following vaccination may not depend on the number of T cells produced directly by the vaccine, but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process...To achieve therapeutic success, investigators will probably need to understand the cause of the local immunosuppression in the tumors and find counteracting agents. As stated above, the list of possible immunosuppressive agents present in tumors is considerable. But it will be important to find whether, for each type of tumor, there is a prevalent immunosuppressive agent. Just as many types of tumors have preferred oncogenic pathways that differ from one type of tumor to another, each type of tumor may also have preferred immunosuppressive processes that we must identify to achieve therapeutic success...Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment...We do not believe that melanoma patients suffer from a degree of general immunosuppression, which we believe is restricted to very late-stage patients who are not included in most studies...Therefore, the difference in the quality of the response would be due to a chance event determining, for instance, the functional properties of the unique or the few responder T cell clones elicited by the vaccine. In that case, it will be essential to understand what this crucial functional property is. At the other extreme, the antivaccine T cell responses would be similar in all patients, but the level of resistance of the tumors would vary considerably. In that case investigators would need to identify the main component of this resistance and find ways to counteract it." (especially pages 193-194).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See *In re Wands* 8 USPQ2d 1400 (CAFC 1988).

Applicant does not argue this rejection.

It is noted by the Examiner that the instant specification discloses use of the claimed peptide as a diagnostic marker (paragraph spanning pages 25-26 of the instant specification.)

8. Claims 1 and 3 are objected to because of the following informalities:

Claim 1 recites SEQ ID NO that are in non-elected groups, and claim 3 also incorporates the SEQ ID NO that are in non-elected groups since it recites "wherein the tumor antigen consists of a peptide of claim 1." Appropriate correction is required.

9. SEQ ID NO: 1-3 appear to be free of the prior art.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 29, 2007

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